DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 2, 2009 and March 19, 2010 have been considered.

2. The Restriction requirement mailed January 19, 2010 has been rendered moot by applicant's claim amendments filed March 19, 2010 and thus it is hereby withdrawn.

   Claims 62 and 65 have been amended.

   Claims 66-72, 76 and 77 are new.

   Claims 62-72, 76 and 77 are pending.

3. The previous grounds of rejection can be found in the Office Action mailed July 31, 2009.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 62, 64 and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421), essentially for the reasons of record as put forth in the prior Office Action mailed July 31, 2009 and as further described below.

   Applicant argues the claims are non-obvious because applicant alleges it would have been unpredictable to one of ordinary skill in the art that an F(ab')2 antibody administered directly to the eye of a corneal transplant patient can penetrate the layers of a transplanted cornea, and thus, presumably applicant is arguing that one of ordinary skill in the art would not have had a reasonable expectation of successfully practicing the claimed invention even after taking into consideration the teachings of the applied references. (see Remarks page 7-8 bridging paragraph to page 9).

   Applicant further argues that even if a prima facie case of obviousness has been established, "Exhibit F provides data showing that treatment with anti-TNFa F(ab')2 fragments significantly and unexpectedly increases graft cornea survival *(see* Figure 1) and decreases

the morphological properties of the cornea associated with graft rejection *(see* Figure 2). Furthermore, it is Dr. Paniagua-Solis' opinion that the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner." Based on this argument it is applicant's position that any prima facie case of obviousness has been negated.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 31, 2009 and for the reasons given below.

With respect to the prima facie obviousness of the claimed invention, applicant's argument is not found convincing for several reasons.

First, applicant describes the structure of the corneal layer of the eye and then concludes that while topical administration is an alternative to systemic administration, "...one of skill in the art would have understood at the time the present application was filed that the cornea is an effective barrier to topical penetration, because the corneal epithelium has annular tight junctions which surround the corneal epithelium. *See id.* Additionally, one of ordinary skill would have understood that topically applied drugs are rapidly eliminated from the pre-corneal area. *See id.*"

However, the reference cited by applicant in support of their conclusions about "topical penetration" and drug elimination from the "pre-corneal area" has not been provided, rather only the abstract for this reference was provided (See Exhibit B, Sasaki et al.). In this regard it is noted that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), See MPEP § 2145.

Nevertheless, even from the non-detailed information that can be gleaned from the Sasaki et al. abstract provided by applicant it is not clear that this reference truly support applicant's argument that one of ordinary skill in the art would not have had a reasonable expectation of successfully practicing the claimed invention even after taking into consideration the teachings of the applied references.

For example, the claimed invention involves the treatment of corneal transplant rejection patient, and as would be well known to one of ordinary skill in the art the surgical procedure for corneal transplantation involves trephining of both the donor and recipient cornea and suturing of the donor cornea onto the trephined recipient cornea (see, e.g., the Merck Manual of Diagnosis and Therapy, Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, page 723, left column, last paragraph). Thus, unlike the case of a healthy cornea a hole has been cut in the recipient cornea and this hole has been covered with the donor cornea, the two layers being attached by sutures. Accordingly, it

would not be surprising to one of ordinary skill in the art if a therapeutic molecule could pass through a transplant recipients cornea more readily than an intact cornea.

Furthermore, it worth noting that the instant claims encompass in their breadth the use of opthalmically acceptable carriers, including dermatologically acceptable gel vehicles, and such a practice has been demonstrated by the cited prior art to increase the delivery of drugs to the cornea. For example, Reza Dana teaches the administration of TNFR-Fc in a vehicle containing sodium hyaluronate which increases viscosity and drug delivery to the surface epithelium (see Dana, e.g., at page 5-6 bridging paragraph; page 9, 1st paragraph; the paragraph bridging pages 17-18 and claim 8).

Applicant then goes on to argue that tumors are physiologically different from other tissues, again citing a number of references in support of their assertions about the unique physiology of tumors but providing no copies of the actual articles being cited (see Remarks page 8-9 bridging paragraph).

Based on this applicant concludes: "one of ordinary skill in the art would have considered the ability of a F(ab')2 antibody to penetrate the cornea differently than the ability of a F(ab')2 antibody because of the differences in tumor physiology compared to non-tumor tissue. Thus, one of ordinary skill in the art would not have necessarily expected that the improved penetration of F(ab')2 fragments into tumor tissue disclosed in Horwitz would apply to the penetration of F(ab')2 fragments into non-tumor tissues such as cornea tissue."

Applicant's assertions and conclusion are not found convincing. First, as stated above arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), See MPEP § 2145.

That said, even if, arguendo, F(ab')2 were especially good at penetrating tumor tissues and not non-tumor tissues (note that based on applicant's non-substantiated arguments about tumor physiology one of ordinary skill in the art would most likely guess the opposite is true, i.e., that F(ab')2 would penetrate non-tumor tissue *even better* than tumor tissue), this would *still* not overcome the prima facie case of obviousness because as put forth in the previous Office Action at page 3, 6th and 7th paragraphs, "…why would one of ordinary skill in the art consider corneal penetration unpredictable, especially so when a larger TNFα antagonist that binds FcR, such as the TNFR-Fc antagonist exemplified by Reza Dana (@150 kDa vs. @100 kDa), is capable of treating corneal transplant rejection in a mouse model?"

As to applicant's argument that the Declaration of Dr. Paniagua-Solis demonstrates significant and unexpected results that overcome any prima facie case of obviousness in view of the cited references this is also not found convincing.

In his declaration Dr. Paniagua-Solis describes an experiment where the effectiveness of topical anti-TNFα F(ab')2 on murine corneal graft rejection was tested. Based on the

effectiveness of topical anti-TNFα F(ab')2 in these experiments Dr. Paniagua-Solis asserts: "It is my opinion that the increased graft cornea survival and decreased morphological properties of the cornea associated with graft rejection would not have been expected in view of the art cited by the Examiner."

Based on this argument applicant's takes the position that any prima facie case of obviousness has been negated.

However, this is not found convincing because other than stating that in his opinion the results of the experiments presented in his declaration were unexpected, Dr. Paniagua-Solis makes no case why he found these results to be unexpected or why the art as whole at his time of invention would have found these results to be unexpected. While Dr. Paniagua-Solis opinion is acknowledged, when Applicant's arguments and the Declaration of Dr. Paniagua-Solis are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims stand rejected as unpatentable over Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana.

6. Claim 63 stands rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324), Adair et al. (EP 0 516 785 B1), Looareesuwan et al. (Am J Trop Med Hyg. 1999 Jul;61(1):26-33, cited herewith) and Reza Dana (WO 00/27421), essentially for the reasons of record as put forth in the Office Action mailed July 31, 2009 and as further described in Section 5 above.

   Applicant argues claim 63 is not obvious for the same reasons that claim 62 is not obvious as put forth in Section 5 above.

   Applicant's argument has been considered but has not been found convincing essentially for the reasons of record as put forth in the Office Action mailed July 31, 2009 and as further described in Section 5 above.

   A New Grounds of Rejection follows.

7. Claims 66-72, 76 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO

92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421) as applied to claims 62, 64 and 65 above, and further in view of the Merck Manual of Diagnosis and Therapy (Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, pages 722-24) and Gerald DeVries (US 2003/0180294).

The teachings of Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana as they relate to claims 62, 64 and 65 were given in the non-final Office Action mailed September 15, 2008 as well as the Office Action mailed July 31, 2009.

Additionally, as to the dosing limitations, i.e., the F(ab')2 antibody dosage concentration and frequency limitations of the new claims, Pluenneke, Dana and Fabrizio, in the context of TNFR:Fc/intact anti-TNFα (Pluenneke and Dana) or F(ab')2 anti-TNFα antibodies (Fabrizio), teach that these TNFα antagonists should be administered at concentration and frequency according to a variety of considerations such as patient response to treatment and the nature of the inflammation to be ameliorated, e.g., acute or chronic, all of which are within the realm of knowledge of a physician of ordinary skill in the art (see Pluenneke at page 4- page 5, left col.; Dana at page 9-10 bridging paragraph and Fabrizio at page 5-6 bridging paragraph). Notably, Dana also teaches treatment of a mouse corneal transplant model system with TNFR-Fc topically administered 24 hours after transplantation and three times/day for the following 8 weeks (see page 17-18 bridging paragraph).

However, while Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana teach some of the specific dosing regimens recited in the instant claims they do not explicitly teach all of the dosing regimens recited, moreover, they do not explicitly teach the administration of the antibody fragments in a dermatologically acceptable gel/semi-solid vehicle.

However, as would be obvious to one of ordinary skill in the art, the administration of the anti-TNFα F(ab')2 both immediately following corneal transplantation as well as the weeks that follow is consistent with art recognized treatment using other immunosuppressants such as corticosteroids as described in the Merck Manual at page 723, right col.

Thus, it is evident from the reference teachings that dosage and frequency of anti-TNFα F(ab')2 administration would be considered by one of ordinary skill in the art to be results effective variables subject to routine optimization. In this regard it is noted that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), and see M.P.E.P. § 2144.05 II.A. Moreover, it is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272,276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804,809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

Lastly, with respect to the limitation that the antibody be present in a "gel" or "semi-solid vehicle", this would have been an obvious way for one of ordinary skill in the art to formulate an antibody for topical administration to the eye consistent with the teachings, e.g., of DeVries at page 11, paragraphs [0087] - page 12, paragraph [0099]. Notably, DeVries also teaches that therapeutic regimens for the treatment of corneal allograft inflammation is a results effective variable subject to routine optimization (see ibid).

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644